of ordinary skill in the art would have been motivated to combine the teachings and suggestions in the art with an expected result of a stable potassium-binding particle useful in treating various renal disorders.[1]

Applicants respectfully submit that the pending claims are patentable under 35 U.S.C. § 103 over the cited references.

Claim 3

Claim 3 is directed to a pharmaceutical composition; this composition comprises core-shell particles having a core component and a shell component. The core component comprises a potassium-binding cation exchange polymer. The shell component comprises a crosslinked polymer that has permeability for potassium ion that is higher than the permeability for a competing cation, is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject, and has a thickness ranging from about 0.002 microns to about 50 microns.

Applicants have identified a variety of core-shell particles particularly appropriate for binding and removing potassium from the gastrointestinal tract. Generally, because of the higher charge of divalent cations, cation exchange polymers have a higher binding avidity for divalent cations over monovalent cations at equilibrium (without regard to exchange kinetics). To efficiently bind and remove a monovalent cation such as potassium from the gastrointestinal tract, a core-shell particle can comprise a shell polymer that preferentially reduces the rate of divalent cation exchange as compared to monovalent cation exchange. Core-shell particles that exchange monovalent cations significantly faster than divalent cations can effectively remove potassium because the core-shell particles will efficiently load with sodium ion (*e.g.,* in the ileum), and then exchange potassium, a monovalent cation, for sodium during transit through the colon, with such monovalent exchange being on a much shorter time frame than competing divalent cation exchange during such transit. Notably, as detailed in Table 1 below, the potassium ion concentration is highest in the sigmoid colon at the end of the gastrointestinal

[1] See Office action dated November 1, 2006 at page 5.

tract, allowing for the core-shell particles to exchange potassium onto the particles, and then remove potassium upon excretion of the core-shell particles in the feces.

TABLE 1	[Na+]	[K+]	[Mg++]	[Ca++]	pH
Stomach*	~30 mM	~15 mM	~5 mM	~10 mM	2-6
Ileum	~120 mM	~5 mM	~10-50 mM	~10-50 mM	7-7.5
Sigmoid Colon	~ 30 mM	~75 mM	~20-40 mM	~10-40 mM	6-7.5

* values are diet dependent; reported ranges based on US average diet.[2]

One way to impart the properties described above to core-shell particles is to control the shell thickness. Applicants have identified shell thicknesses which meaningfully contribute to balancing competing functional characteristics of the shell polymer. For example, core-shell particles can advantageously have a shell that is thick enough to meaningfully reduce the permeability of the shell polymer for divalent cations. Also, core-shell particles can have shells thin enough to maintain an acceptably high permeability rate for monovalent cations.

Notenbomer generally discloses methods and particles for binding monovalent cations. The particles have a nucleus and a coating; the nucleus contains a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and polyethyleneimine. These particles are used to treat hypertension. Notenbomer does not describe nor provide data that allows for the calculation of the thickness of the coating material.

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[2] *See, e.g.,* Ross, E. J. *et al.* "Observations on cation exchange resins in the small and large intestines." Clin Sci (Lond) **13**(4): 555-66 (1954); *see also* Spencer, A. G. *et al.*,"Cation exchange in the gastrointestinal tract." Br Med J **4862**: 603-6 (1954); *See, e.g.,* Wrong, O., A. *et al.,* "In Vivo Dialysis of Faeces as a Method of Stool Analysis. I. Technique and Results in Normal Subjects." Clin Sci 28: 357-75 (1965); *see also* Wrong, O. M., "Role of the human colon in Homeostasis." Scientific Basis of Medicine: 192-215 (1971); *see also* Salas-Coll, C. A. *et al.,* "Potassium transport across the distal colon in man." Clin Sci Mol Med 51(3): 287-96 (1976); *see also* Agarwal, R., R. *et al.,* "Pathophysiology of potassium absorption and secretion by the human intestine." Gastroenterology 107(2): 548-71 (1994).

Kelly *et al*. generally disclose coatings to provide corrosion resistance to metal substrates. Kelly *et al*.'s corrosion-resistant coatings include a polymeric matrix as a continuous phase, and polyaniline particles dispersed throughout the matrix.. The polyaniline particles, in turn, contain a core polymer having strong acid groups and a polyaniline polymer attached to the core polymer. To the extent Kelly *et al*. disclose core-shell particles, the core-shell particles consist of a core polymer particle and a "polyaniline polymer form[ing] a shell completely encompassing the core polymer particle."[3] Significantly, Kelly *et al*. do not disclose core-shell *particles* in which a crosslinked polymer forms a shell around the core. Kelly *et al.* also do not describe pharmaceutical compositions, nor do they describe shell components that comprise a crosslinked polymer.

The Office has failed to establish *prima facie* obviousness because the cited references do not disclose, alone or in combination, all of the features of claim 3. Neither Notenbomer nor Kelly *et al*. disclose a core-shell particle comprising a shell component, where the shell component comprises a crosslinked polymer and has a thickness ranging from about 0.002 microns to about 50 microns.

The Office has also failed to establish *prima facie* obviousness because it has failed to show that a skilled person would have considered combining the Notenbomer and Kelly *et al*. disclosures to arrive at the compositions of claim 3. Kelly *et al*.'s composition is not a pharmaceutical composition and the polyaniline shell described by Kelly *et al*. has a completely different purpose than the shell component of the claimed compositions. The Kelly *et al*. reference is not in the field of applicant's endeavor and there is no reason of record why a person of ordinary skill would have found Kelly *et al*.'s disclosure pertinent. Since Kelly *et al*. is non-analogous art, Kelly *et al*. cannot be properly combined with Notenbomer to support a rejection of claim 3. Accordingly, claim 3 and the claims that depend therefrom, are patentable in view of the cited references.

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[3] Kelly et al. at paragraph [0028].

Claim 53

Claim 53 is directed to a pharmaceutical composition; this composition comprises core-shell particles having a core component and a shell component. The core component comprises a potassium-binding cation exchange polymer. The shell component comprises a crosslinked polymer that has a permeability for potassium ion that is higher than the permeability for a competing cation, is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject, and the weight ratio of the shell component polymer to the core component polymer ranges from about 0.0001:1 to about 0.5:1.

The Office has failed to establish *prima facie* obviousness. Notenbomer does not disclose the weight ratio of the shell component polymer to the core component polymer of the disclosed core-shell particles and Notenbomer fails to disclose sufficient information to enable a person of ordinary skill to calculate the shell to core weight ratio. Kelly *et al.* disclose coatings to provide corrosion resistance to metal substrates and the Office has not, and indeed cannot, articulate any reason a person of ordinary skill would consider any aspect of Kelly *et al.*'s core-shell particles, including shell to core weight ratio, somehow pertinent to those working in the pharmaceutical art, particularly when Notenbomer fails to consider this parameter sufficiently pertinent to even mention. Accordingly, claim 53 and the claims that depend therefrom, are patentable in view of the cited references.

Claim 34

Claim 34 is directed to a method of treating an animal subject wherein the treatment comprises administering an effective amount of the pharmaceutical composition of claim 3 or claim 53 to an animal subject in need of such treatment. Further, claim 36 depends on claim 34 and is directed to a method for treating renal insufficiency, renal failure, end stage renal disease (ESRD) and combinations thereof.

The disclosure of Notenbomer is described above in connection with claim 3. Notenbomer does not describe nor provide data that allows for the calculation of the shell thickness nor the weight ratio of the coating to the nucleus. Notenbomer also fails to disclose methods for treating renal insufficiency, renal failure, and end stage renal disease (ESRD).

The Kelly *et al.* disclosure is described above in connection with claim 3. Kelly *et al.* fails to describe pharmaceutical compositions, methods of treatment, and shell components that comprise a crosslinked polymer.

The Office has failed to establish *prima facie* obviousness for the reasons detailed above for claims 3 and 53. Further, the combined disclosures would not have led a person of ordinary skill to the invention defined by claim 36 because neither Notenbomer nor Kelly *et al.* disclose methods for treating renal insufficiency, renal failure, and end stage renal disease (ESRD). Although the Notenbomer particles could have been used to bind potassium in some subjects, it would not have been obvious to a person of ordinary skill to modify the particles and use such particles in subjects suffering from renal insufficiency or renal failure.Notably, such subjects suffering from renal insufficiency or renal failure typically can have a relatively long time for residence and passage through their gastrointestinal tract. Kelly *et al.*, which does not disclose pharmaceutical compositions or therapeutic uses, and is from a non-analogous art, does not provide further motivation in this regard. Therefore, claims 34, 36, and the claims that depend therefrom are patentable in view of the cited references.

Provisional Double Patenting Rejection

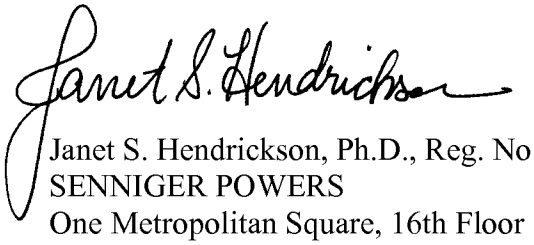
The Office provisionally rejects claims 3, 4, 14, 15, 18-22, 29, 30, 34, 36, 40, and 51-75 on the ground of nonstatutory obvious-type double patenting over claims 1, 10, 16, 17, 20-24, 31, 32, and 45-65 of copending U.S. Serial No. 10/813,872. Without conceding the propriety of this rejection, applicant will consider filing a terminal disclaimer to obviate this basis for rejection when the application is otherwise in condition for allowance.

CONCLUSION

Applicant submits that the present application is now in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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